AD_____

CONTRACT NUMBER: DAMD17-94-C-4081

TITLE: Fluorescence Optic Fiber Stereotactic Needle Ratiometer for Breast Tumor Diagnosis

PRINCIPAL INVESTIGATOR: Doctor Guichen C. Tang

CONTRACTING ORGANIZATION: Mediscience Technology Corporation
Cherry Hill, New Jersey 08003

REPORT DATE: October 1995

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1995	Annual 23 Sep 94 - 22 Sep 95

4. TITLE AND SUBTITLE
Fluorescence Optic Fiber Stereotactic Needle Ratiometer for Breast Tumor Diagnosis

5. FUNDING NUMBERS
DAMD17-94-C-4081

6. AUTHOR(S)
Doctor Guichen C. Tang

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Mediscience Technology Corporation
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Activities during the first year focused on engineering the optic fiber probe and needle, on the breadboard design of the fluorescence instrument and on establishing the clinical protocol and patient consent form that must be followed in the clinical feasibility study part of the project. Fabrication of the device and trials on patients could not be undertaken in the absence of approval by the cooperating clinic's (Mass. Gen. Hospital) Institutional Review Board ("IRB"). The constraints on the progress of the approval centered around the careful and protracted review by the IRB which has just recently granted approval based on its acquiescence that the device is of nonsignificant risk ("NSR") for the intended application. Still awaited from the IRB are revisions in their Patient Consent Form to be resubmitted to the Human Use Review and Regulatory Affairs Division, HQ, USARMRMC.

14. SUBJECT TERMS
Fluorescence, Fiber, Optic, Ratiometer, Needle, Biopsy, Tumor, Cancer
Breast Cancer

15. NUMBER OF PAGES
18

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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FOREWORD

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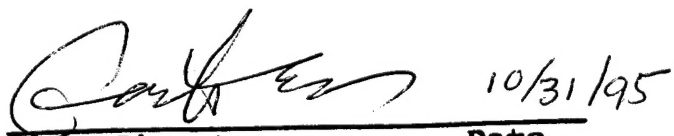
 10/31/95

PI - Signature Date

4. Contents

5. Introduction

It is well known that mammographic screening of asymptomatic women can detect breast cancer early and can result in a reduction of mortality. Despite mammography's ability to find breast cancer at an early stage, benign and malignant lesions may have similar morphology [1]. Until recently, performing a biopsy was the only certain way to distinguish between a benign and malignant tumor. Biopsy is a surgical procedure carried out in a hospital, and is tedious, time consuming, and expensive. Most biopsies are found to be benign [2]. A novel real time examination method in situ is of critical importance. Fluorescence Optic Fiber Stereotactic Needle Ratiometer for Beast Tumor Diagnosis (CD-Ratiometer) is an approach to improve the diagnosis of tissue. Mediscience's CD-Scan which has been used to measure the emission, excitation, and synchronized scan of human tissue in vitro shows spectroscopic differences [3-6] between diseased and benign tissue. A compact bread board CD-Ratiometer measures the ratio of the fluorescence intensities at two predetermined wavelengths emitted from human tissues photoexcited by a predetermined wavelength from a light source.

The purpose of this project is to develop a modified CD-Ratiometer equipped with a small diameter optic fiber to enter a hollow metallic needle for in vivo breast tumor diagnosis. The unit will be tested at Massachusetts General Hospital. The CD-Ratiometer will give a breast tissue diagnosis in real time, and so greatly shorten the time for clinical results that normally are obtained from biopsy and pathology.

The device, through its needle-fiber optic probe, will deliver an excitation light beam onto a breast tumor and collect fluorescence from the tumor back to photo detectors through a set of narrow band filters for data analysis.

6. Body

Two tasks were accomplished during this period. The study protocol was approved by the IRB at MGH, and an optic fiber needle design was completed.

(1) Optic fiber Needle

A schematic diagram of a version of the CD-Ratiometer that may be used for breast cancer diagnosis in vivo is shown in Fig.1. The excitation light from a source will pass through an optical filter. It will be collimated by a collimator and pass through a filter mounted on a filter wheel and a chopper. The light will be focused onto the input end of the excitation fiber. The light passes through the fiber and arrives at the dichroic mirror which has a high reflection at 300 nm and high transmission from 340 nm to 520 nm. After being reflected by the dichroic mirror, the excitation light will pass through the optic fiber probe, and onto the breast tissue. The fluorescence, or scattered excitation light arriving back from the breast tissue will be collected by the same probe and pass through the dichroic mirror. The fluorescence, or scattering excitation light will be split into two equal intensity beams by a beam splitter. The one beam passing through the beam splitter will be detected by the first photomultiplier (PMT#1) after passing through the detection filter on the filter wheel pre-set for the desired wavelength. The beam reflected by the mirror will be detected by PMT #2 after passing through the the second detection filter on another filter wheel for the second pre-set wavelength. The signals from the two PMTs will be amplified by two lock-in amplifiers, and a spectral intensity ratio will be calculated by a PC computer.

Fig.2 shows how the optic fiber probe is to work with the hypodermic needle. A 90° side view fiber probe (Fig.2a) with an outside diameter (O.D.) of 0.559 mm (24 gauge) is inserted freely in a hypodermic needle (Fig.2b) with an inside diameter (I.D.) of 0.585 mm. and an outside diameter of 0.902 mm (20 gauge). The needle (a so-called "side firing needle") is slotted to match the location of the 90° view giving a periscope effect. The combination configuration is shown in Fig.2c.

The critical element of the CD-Ratiometer is the optic fiber probe designed to deliver an excitation light beam onto a breast tumor and collect fluorescence from the tumor back to detectors through a set of narrow band filters for data analysis.

The detailed design of the side-firing fiber probe now completed is shown in Fig.3. A multimode fiber with a 0.25 mm outside diameter (O.D) is assembled into a stainless steel (S.S.) needle tubing with an outside diameter of 24 gauge (0.559 mm, O.D.). The fiber face in the metal tubing is polished perpendicular to the needle axis $\pm$ 1°. A 45° mirror will be plugged into the metal

tubing at its end. The light, either excitation beam or fluorescence, passes through in or out from the side window of the side firing needle. A copy of the photograph of this effect is shown in Fig.4. The needle concept was suggested by investigators at Massachusetts General Hospital. Its advantage is that 360° measurements can be made by rotating the needle.

The outside diameter of the optic fiber needle used was determined by the clinical investigators at Massachusetts General Hospital. Preliminary measurements will be under way to test an older version CD-Ratiometer for appropriate signal to noise ratio.

(2) IRB

Based on a review by their Subcommittee on Human Studies, dated 4/11/95, the Institutional Review Board (IRB) of Massachusetts General Hospital (MGH) furnished a protocol and patient consent form which were appended to HHS Form 310. These were submitted to USARMRMC on 6/5/95 (Appendix 2). Compliance with 45 CFR 46 and OPRR Assurance had been submitted earlier. The late timing of the IRB review was attributed to thorough diligence and a scheduling backlog.

The Sponsor was notified 7/3/95 by the Human Use Review and Regulatory Affairs Division with questions and specified revisions that were required in the patient consent form. MGH was informed by letters, 7/12 and 7/19, and provided with annotated suggestions for revisions (Appendices 3 & 4). The revised patient consent forms are awaited from MGH.

Additionally, directly answerable replies to questions were satisfactorily discussed verbally with the Human Use Review Division. These were drafted in a cover letter (Appendix 5) which will be submitted with the revised patient consent forms.

7. Conclusion

The main designs of the unit are completed. Some optical fiber needle probes have been designed. Parts for ratiometer and fibers are ready to be ordered. The human breast test protocol in vivo has recently been approved at Massachusetts General Hospital.

Chicken tissues will be used to calibrate the unit for sensitivity and noise. Then breast tissue specimens will be obtained from MGH for initial instrument calibration of different tissue characteristics, eg. fat, glandular, and fibrous.

8. References

1. D.B.Kopans and C.A.Swann, Preoperative imaging-guided needle placement and localization of clinically occult breast lesions, AJR, 152:1-9, January, 1989.

2. W.J.Gallagher, G.Gaerdenosa, J.R.Rubens, K.A.McCarthy, and D.B.Kopans, Minimal-volume excision of non palpable breast lesions, AJR, 153:957-961, 1989.

3. R.R.Alfano, G.C.Tang, A.Pradhan, W.Lam, D.S.J.Choy, and E.Opher, Fluorescence spectra from cancerous and normal human breast tissues, IEEE J, Quantum Electron. QE-23, 1806-1811, 1987.

4. G.C.Tang, A.Pradhan, and R.R.Alfano, Spectroscopic differences between human cancerous and normal lung and breast tissues, Lasers in Surgery and Medicine, 9:290-295, 1989.

5. R.R.Alfano, B.B.Das, J.Cleary, R.Prudente, B.J.Celmer, Bull. N. Y. Acad. Med., Light sheds light on cancer---distinguishing malignant tumors from benign tissues and tumors, Second series, 67(2):143, 1991.

6. Yuanlong Yang, A.Katz, E.J.Celmer, M.Z.Szczepaniak, and R.R.Alfano, Optical spectroscopy of benign and malignant breast tissues, Being submitted to Biomedical Journal, 1995.

9. Figure Captions

Fig.1 Schematic diagram of optic system for the optical fiber needle CD-Ratiometer

Fig.2 Diagram of combination of an optic fiber probe with a hypodermic needle

Fig.3 Design of 24 gauge O.D. side-firing fiber probe.

Fig.4 Photocopy of a 20 gauge O.D. hypodermic needle with a 90° exit hole.

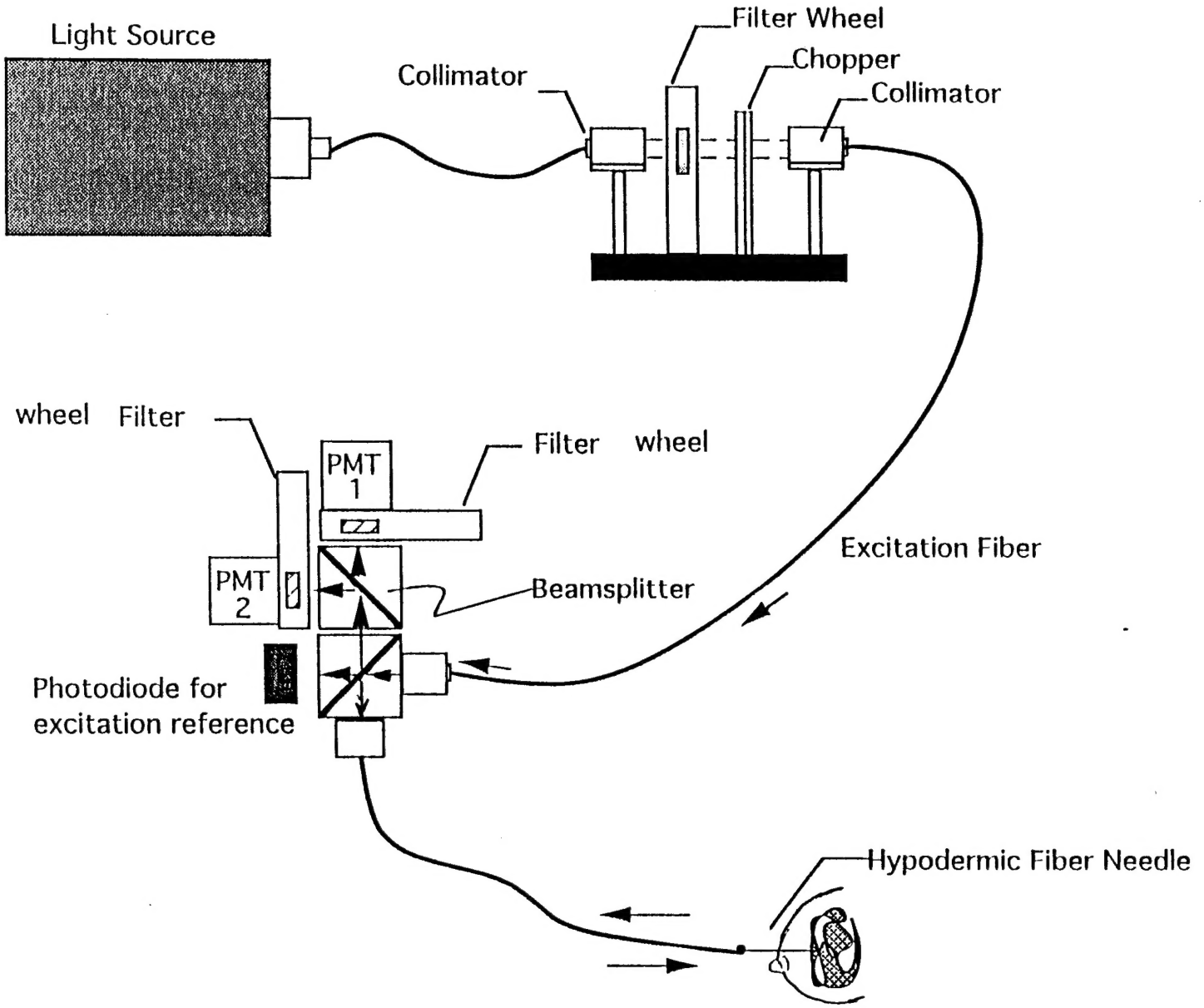
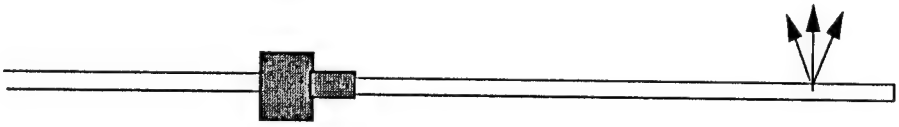
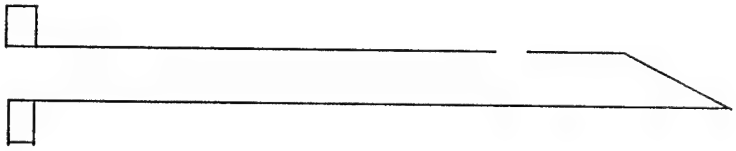

Light Source
Collimator
Filter Wheel
Chopper
Collimator
wheel Filter
Filter wheel
PMT 1
PMT 2
Beamsplitter
Excitation Fiber
Photodiode for excitation reference
Hypodermic Fiber Needle

Fig. 1

(a) 90 side firing optic fiber probe (24 gauge) O.D. (0.559 mm)



(b) Hypodermic needle (20gauge) O.D.(0.902 mm); I.D.(0.585mm)



(c) Fiber probe is freely inserted in hypodermic needle

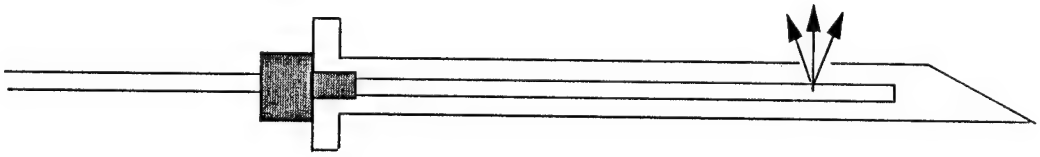
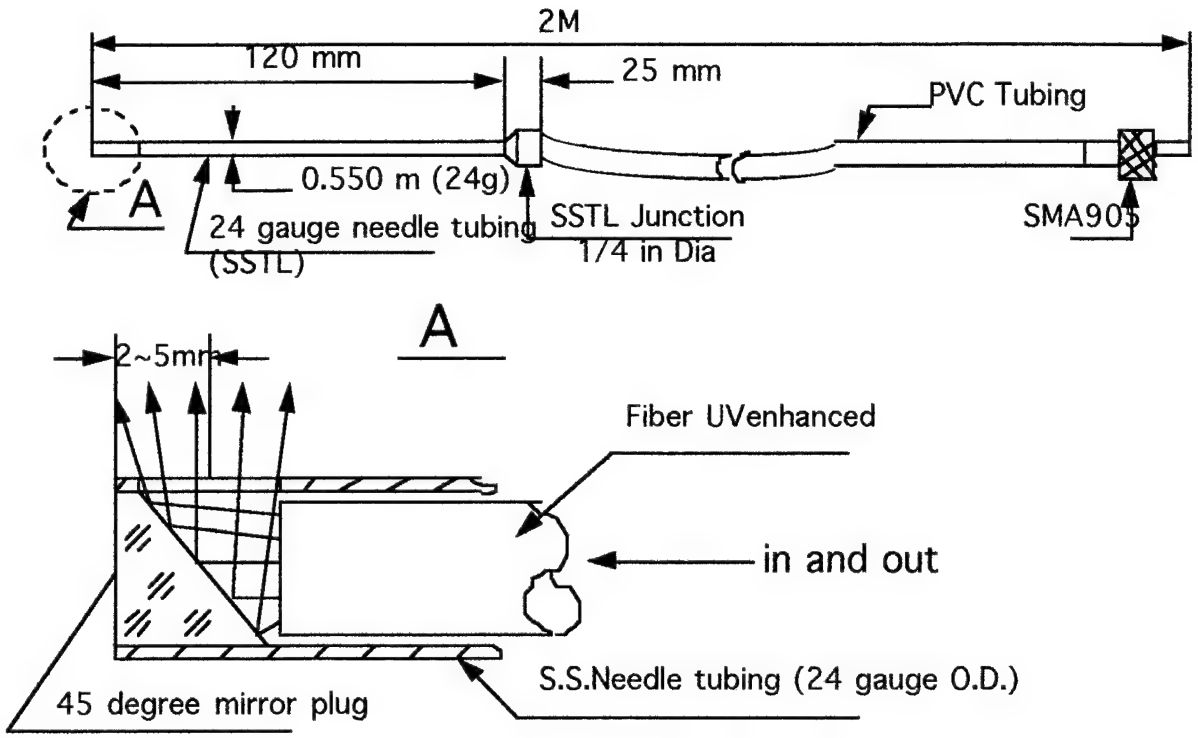


Fig. 2



1) Fiber faces are polished to a scratch-free finish at 40x magnification

2) Fiber type UV enhanced multimode 0.3 mm

Side-firing fiber needle probe

Fig. 3

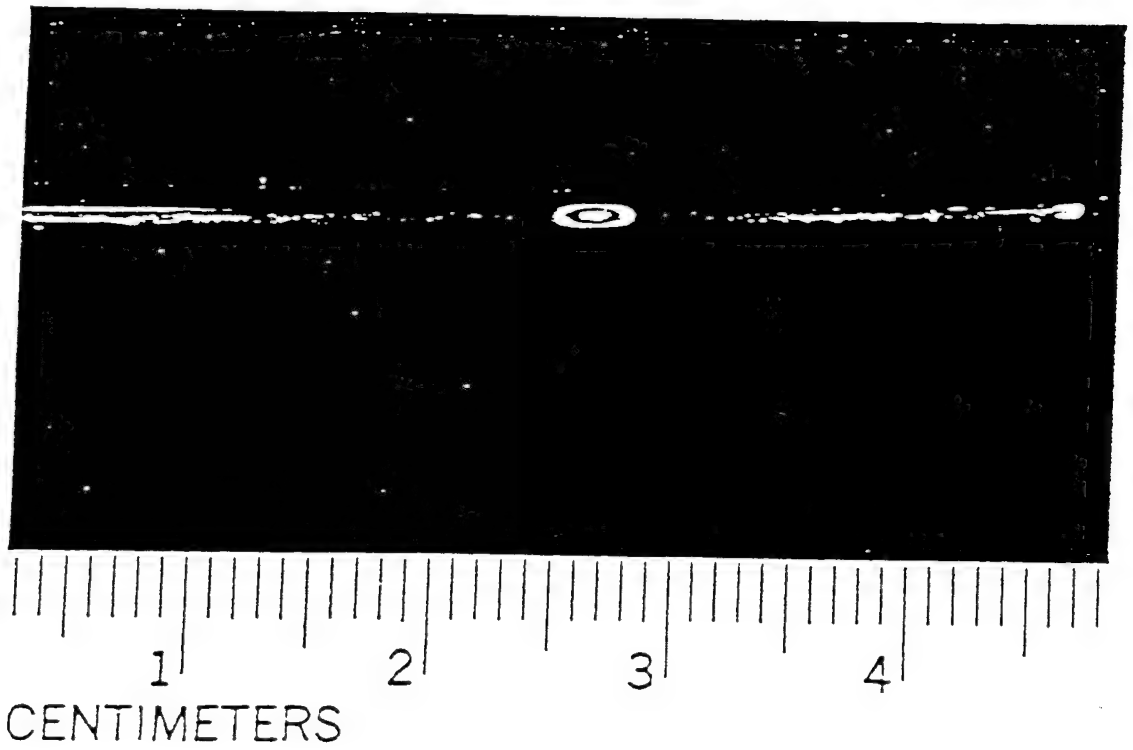


Fig. 4

Appendix 1

MEDISCIENCE TECHNOLOGY CORP.

P.O. Box 598, Woodcrest
Cherry Hill, NJ 08003
Telephone 609 428 7952
Facsimile 609 428 2692

49 Willow Place
Albertson, NY 11507
Telephone 516 484 9141
Facsimile 516 484 4795

to: George Brown
from: Ronald Krumm via fax 301 619 2937
date: 12/13/94
re: Acceleration of Project - Contract DAMD17-94-C-4801
cc: P. Katevatis, R. Alfano

Confirming our conversation, Mediscience would like to accelerate the work on the Fiberoptic Needle Biopsy device. Guichen Tang, who is the P.I. and working 50% of his time on the project, also is working 50% of his time on another funded project that will come to an end in six months.

Mediscience would like Tang to devote 100% of his time on the DAMD project when the other project ends in order to accelerate our progress. Accordingly, we would propose to pay him at twice the rate over the ensuing nine months (ie. months 7-15) which would amount to the same total salary support as budgeted.

Please let me know if this is acceptable.

Approved
12 Sep 95
Kathy A Hockley
Contract Specialist

MEDISCIENCE TECHNOLOGY CORP.

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June 5, 1995

Ms. Catherine A. Smith
Office of the Deputy Chief of Staff
for Regulatory Compliance & Quality
HQ, USARMRMC
Fort Detrick
Frederick, MD 21702-5012

via fax 301 619 7803
and mail

Re: BAA "IDEA" Proposal, Fluorescence Optic Fiber Stereotactic Needle Ratiometer for Breast Tumor Diagnosis, USARMDC Proposal Log No. B4339210 (HURRAD Log A-6297)
Contract DAMD17-94-C-4801

Dear Ms. Smith:

I have enclosed under separate cover an original signed copy of Form 310 appended to which is the signed IRB approval with protocol and patient consent forms from Massachusetts General Hospital, the cooperating clinic. Their letter, dated 10/6/93, stating their compliance with 45 CFR 46 and OPRR Assurance Number M1331, IRB number 01, also is attached.

Please let us know if anything further is required.

Yours Sincerely,

s/

Ronald W. Krumm (NY)
V.P. Mktg & Development

cc: R. Alfano
P. Katevatis
G.Tang

Alan Becker, DCAA via fax 609 354 7520
George B.Brown, USARMDC via fax 301 619 2937
G. Whitman, M.D., M.G.H. via fax 617 726 1074 w/att.

Appendix 3

MEDISCIENCE TECHNOLOGY CORP.

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Telephone 516 484 9141
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July 12, 1995

Gary J. Whitman, M.D.
Massachusetts General Hospital
Department of Radiology
Boston, MA 02114

via fax 617 726 1074
and mail w/enclosures

Dear Dr. Whitman:

Re: In Vivo Measurement of Auto Fluorescence Spectra Within Mammographically Detected Breast Lesions

We have received the enclosed letter, dated July 3rd with a number of questions and requests for additional information from the Army in connection with your protocol and patient consent form. Subsequently, I had a useful and cordial conversation with Kathleen Dennis, the author, and I have begun to draft a response (first page attached). Their request is less onerous than I first thought.

Certain inputs are needed from you, such as a revised patient consent form. Also, there is a Form 60-R, entitled, Volunteer Registry Data Sheet (30 copies enclosed) required by the Army to be submitted for each and every volunteer at the end of the study. When you receive the materials please call to discuss.

Yours sincerely,

R.W. Krumm

cc: R. Alfano
P. Katevatis
G.Tang

MEDISCIENCE TECHNOLOGY CORP.

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Facsimile 516 484 4795

July 19, 1995

Gary J. Whitman, M.D.
Massachusetts General Hospital
Department of Radiology
Boston, MA 02114

via fax 617 726 1074
w/att. (9 pages)

Dear Dr. Whitman:

Re: In Vivo Measurement of Auto Fluorescence Spectra Within Mammographically Detected Breast Lesions

Further to my letter to you of July 12 and our conversation yesterday, I have annotated the Medical Research Consent Form with suggested changes in items b(1) - b(9) to satisfy the Army's requests in their 7/3/95 letter.

Items b(10) - b(12) pertain to the Volunteer Registry Data Sheet. The USARMDC's requirement of a completed copy at the end of the study on each volunteer for the Army's records includes the stipulation that these records are maintained in strict confidence "..and not released to anyone." [see page F-5, ¶ (15) of attached Appendix F]. At that time, direct sealed transmittal of the documents can be arranged.

When all of the Army's questions have been addressed to our mutual satisfaction, we will send the reply (text approved by all concerned) with appropriate enclosures along the lines of my draft letter dated July 17 which you have.

I think we have already done most everything substantively and that this is just reformatting. Thanks for helping us with the paper chase.

Sincerely,

R.W. Krumm

cc: R. Alfano
P. Katevatis
G.Tang

MEDISCIENCE TECHNOLOGY CORP.

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DRAFT

MM/DD/ 1995

Ms. Kathleen J. Dennis
Human Use Review and
Regulatory Affairs Division
HQ, USARMRMC
Fort Detrick
Frederick, MD 21702-5012

via fax 301 619 7803

Re: BAA "IDEA" Proposal, Fluorescence Optic Fiber Stereotactic Needle Ratiometer for Breast Tumor Diagnosis, USARMDC Proposal Log No. B4339210 (HURRAD Log A-6297)
Contract DAMD17-94-C-4081

Dear Ms. Dennis:

Regarding your letter of July 3rd concerning the protocol submitted from Massachusetts General Hospital (MGH) entitled "In vivo Measurement of Auto Fluorescence Spectra Within Mammographically Detected Breast Lesions", some of the questions were answerable directly. Others required input including a revised Patient Consent Form from MGH the cooperating clinic.

a. (1) Using 21CFR terminology, we consider this a "Phase I" protocol inasmuch as this is a pre-IDE feasibility study, the purpose of which is to submit an application to FDA for an Investigational Device Exemption pursuant to a subsequent application for Premarket Approval (PMA) based on the clinical data generated during "Phases II and III" under the IDE.

Principal Investigator

a. (2) The P.I. in the employ of Mediscience is Guichen C. Tang whose address is:
c/o
City University of New York
Institute for Ultrafast Spectroscopy and Lasers
Convent Avenue & 138 Street
New York, NY 10031
tel 212 650 5543, fax 212 650 5530

b.(12) The P.I. for the cooperating clinic, MGH, is Gary J. Whitman, M.D., Instr. of Radiology
c/o
Department of Radiology, ACC 2
Massachusetts General Hospital
Boston, MA 02114
tel 617 726 6894, fax 617 726 1074

For the clinical testing (eventually under an IDE), the P.I. must be a physician to be qualified.

a. (3) The address of the study location is MGH as shown above - see letterhead (Exhibit 1).

MEDISCIENCE TECHNOLOGY CORP.

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November 6, 1995

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RMI-S
Building 504
Fort Detrick, Maryland 21702-5012

Re: Annual Report for Contract Number DAMD17-94-C-4081

Dear Sir/Madam:

Enclosed please find an original and five copies of the above cited report. Thank you.

Sincerely,

Ronald W. Krumm (NY)
V.P. Mktg & Development

cc: P. Katevatis
G.Tang